Clinical Neurophysiology 125 (2014) 2207–2211

Contents lists available at ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

A reduction of sleep spindles heralds seizures in focal epilepsy

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ARTICLE INFO

Article history:
Accepted 4 March 2014
Available online 12 March 2014

Keywords:
Sleep
Epilepsy
Epilepsy surgery
Sleep spindle
Seizure prediction

HIGHLIGHTS

- A strong relationship has been noted between sleep spindles and seizure occurrence in patients with temporal and extratemporal lobe epilepsy.
- The reduction of spindle density before secondarily generalized seizures was more pronounced in extratemporal lobe epilepsies than in temporal lobe ones.
- The occurrence of seizures and propensity of seizure generalisation in focal epilepsy is modulated by sleep spindles.

ABSTRACT

Objectives: Sleep has profound effects on epilepsy. It may alter the occurrence of interictal discharges (IEDs) and seizures. Vice versa, an active epilepsy changes sleep. Sleep spindles are typically associated with an increase of IEDs. We examined whether seizures change the number and power of spindles preceding nightly seizures.
Methods: We retrospectively examined the nightly EEG recordings of presurgical epilepsy patients from our EEG-video-monitoring unit. We evaluated the 200 s before the EEG seizure onset for spindle density (spindles per minute) and spindle power and compared that to the interictal baseline sleep.
Results: The spindle density and the spindle power decreased significantly before the first seizure. The reduction before secondarily generalized seizures (8.7 ± 2.5; $p = 0.001$) was more pronounced than before focal seizures (10.5 ± 2.5; $p = 0.003$) compared to baseline (12.2 ± 2.7). This finding was more pronounced in extratemporal lobe epilepsies than in temporal lobe epilepsies. The reduction of spindle power was also significant and was more pronounced in XTLE. These results were consistent for all other seizures during sleep, the mean spindle density decreased significantly in all focal (10.2 ± 1.9; $p = 0.001$) and generalized preictal period (8.8 ± 2.4; $p = 0.001$) compared to the mean interictal period (12.1 ± 2.1). These were also more significant in XTLE than TLE group.
Conclusions: Our data demonstrate that the occurrence of seizures and propensity of seizure generalisation in focal epilepsy is modulated by specific characteristics of light sleep such as sleep spindles.
Significance: This study supports the notion that changes in the epileptic network precede the seizure onset and have an influence on seizure generation and termination.

1. Introduction

Sleep and epilepsy have reciprocal influences on each other. NREM sleep promotes interictal epileptic activity (Sammaritano et al., 1991) and in some epilepsy syndromes, seizures occur in association with the sleep wake cycle (Herman et al., 2001). On the other hand, an active epilepsy will reduce the amount of deep sleep and patients have less refreshing sleep (Xu et al., 2006).

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http://dx.doi.org/10.1016/j.clinph.2014.03.001
1388-2457/

Sleep is not a uniform loss of consciousness, but it is rather a highly dynamic behavioral process, reflected by typical, systematic changes on EEG allowing to score different sleep stages. Sleep spindles are typical EEG sleep pattern, which are thought to reflect a higher level of EEG synchronization, resulting from an increased thalamocortical synchronicity (Steriade et al., 1993). A strong relationship has been noted between these EEG patterns and interictal epileptic activity, with an increase in IEDs during sleep spindles (Shouse, 1987). In contrast, the relationship between spindles and seizures is not well studied. Therefore, we investigated the relationship of spindles to nightly seizures in patients with focal epilepsies.

2. Methods

We retrospectively examined all EEG-video-monitoring records of our patients at the Faculty of Medicine, Hacettepe University from 1999 to 2012 who had been admitted for presurgical evaluation of refractory seizures. We identified 42 patients with secondarily generalized seizures during NREM sleep, with 22 of them also having focal seizures during sleep. Patients with intracranial electrodes were not included.

All patients had their antiepileptic drugs (AEDs) tapered during the monitoring session to facilitate the recording of seizures. For most patients, AEDs were decreased by almost one third at the time of admission, with subsequent further decreases as needed.

The patients were divided into two groups according to the localization of seizure onset: patients with temporal lobe epilepsy (TLE) and extratemporal lobe epilepsy (XTLE). The site of probable seizure onset was determined in an epilepsy case conference by using clinical and electrographic seizure characteristics, supplemented by interictal EEG, clinical history, and results of MRI, PET, and ictal and interictal SPECT, when available. Because most patients did not undergo intracranial EEG recording, these localizations are best estimates of the ictal onset zone.

Continuous video-EEG recordings were performed over 3–10 days with scalp electrodes which were placed according to the International 10–20 System with additional anterior temporal electrodes. Electrooculogram, electrocardiogram and submental electromyogram was included. Sleep stage was determined by the criteria described by Rechtschaffen and Kales (1968).

In the first part of the study, when patients had one and more than one secondarily generalized seizure during sleep, only the first seizure (42 patients) was investigated to exclude the effect of seizures on sleep. In this group if patients had additional focal seizures to secondarily generalized seizures during sleep, their first focal seizure (22 of 42 patients) was also investigated. First seizures during sleep of all patients occurred in the third night or later time of EEG-video-monitoring, except two of them. These two patients had their first seizures in the first night sleep of monitoring. But their last seizures before monitoring were 4–7 days prior, and they did not occur during sleep. So these previous seizures should not affect the sleep. For each subject, the 200 s just before the ictal EEG onset were analyzed for spindle density and spindle power (Fig. 1A). If there was an awakening or an arousal period shortly before the seizure onset, these periods were not included in analyzing the spindle density. Most of the patients had seizures at the beginning of the Non-REM 2 sleep, so we could not select longer time period for analysis. This selected time period is referred to as the "preseizure period". Sleep spindles were scored according to the published criteria as sleep EEG spindles with a frequency between 11 and 16 Hz and a duration >0.5 s (Iber et al., 2007). For baseline comparison, EEG samples of equal duration containing spindles were selected from nights without any seizure and are referred to as the "interictal period" (Fig. 1B). The AED doses had to be the same as in the seizure nights to include those recordings. The spindle density was measured as number of spindles per 60 s. Additionally 200 s of EEG recordings with normal background activity during restful waking of each patient was evaluated to give a baseline for power calculations.

In the second part, to check the consistency within a given patient we also investigated all seizures, when patients had more than one focal or secondarily generalized seizure during sleep. Also for each patient, 4–5 interictal EEG periods containing spindles were selected from nights without any seizure, to compare the baseline-interictal period. The mean of these 4–5 interictal periods are referred to as the "average interictal period".

The spectral power of the spindle band was calculated for nine channels (F3, F4, Fz, C3, C4, Cz, P3, P4 and Pz) after adjusting for the spectral power of the non-spindle baseline. These channels were selected, because two types of spindles are reported topographically, frontal and centro-parietal spindles (Werth et al., 1997).

The spectral analysis was performed on segmented, non-overlapping 2 s EEG samples and artifact rejection was performed automatically on the basis of thresholding. Each single sweep was Hamming-windowed to control for spectral leakage (Gerloff et al., 1998). The power spectra in the range of 11–16 Hz were calculated for each epoch with a minimum of 20 epochs and averaged over the frequency bins. The state dependent power was calculated as the percentage change in the power between the two conditions as follows (Gerloff et al., 1998):

$$\mathrm{SDpower}_{\mathrm{interictal,rest}} = 100 * \left(\mathrm{SDpower}_{\mathrm{interictal}} - \mathrm{SDpower}_{\mathrm{rest}}\right) / \mathrm{SDpower}_{\mathrm{rest}} \quad (1)$$

$$\mathrm{SDpower}_{\mathrm{preseizure,rest}} = 100 * \left(\mathrm{SDpower}_{\mathrm{preseizure}} - \mathrm{SDpower}_{\mathrm{rest}}\right) / \mathrm{SDpower}_{\mathrm{rest}} \quad (2)$$

$$\mathrm{SDpower}_{\mathrm{preseizure,interictal}} = 100 * \left(\mathrm{SDpower}_{\mathrm{preseizure}} - \mathrm{SDpower}_{\mathrm{interictal}}\right) / \mathrm{SDpower}_{\mathrm{interictal}} \quad (3)$$

In order to account for the variance of spectral power estimates a logarithmic transformation was used (Halliday et al., 1995):

$$\log_{10}(\mathrm{SDpower}_{\mathrm{interictal,rest}}) = 100 * \left[\log_{10}(\mathrm{SDpower}_{\mathrm{interictal}}) - \log_{10}(\mathrm{SDpower}_{\mathrm{rest}})\right] / \log_{10}(\mathrm{SDpower}_{\mathrm{rest}}) \quad (4)$$

$$\log_{10}(\mathrm{SDpower}_{\mathrm{preseizure,rest}}) = 100 * \left[\log_{10}(\mathrm{SDpower}_{\mathrm{preseizure}}) - \log_{10}(\mathrm{SDpower}_{\mathrm{rest}})\right] / \log_{10}(\mathrm{SDpower}_{\mathrm{rest}}) \quad (5)$$

$$\log_{10}(\mathrm{SDpower}_{\mathrm{preseizure,interictal}}) = 100 * \left[\log_{10}(\mathrm{SDpower}_{\mathrm{preseizure}}) - \log_{10}(\mathrm{SDpower}_{\mathrm{interictal}})\right] / \log_{10}(\mathrm{SDpower}_{\mathrm{interictal}}) \quad (6)$$

3. Data analysis

Statistical analysis was performed using the SPSS 16.0 (SPSS Inc., Chicago, USA). A *t*-test for independent samples was used for continuous variables. Group results for TLE and XTLE were compared with the Mann–Whitney-*U*-test. The differences in mean of the spindle density and power of spindle waves between interictal and preseizure periods were analyzed with the Wilcoxon Ranking Scale test. Statistical significance was assumed at a *p*-value of less than 0.05, multiple testing was accounted for by a Bonferroni–Holm review but no result had to be rejected.

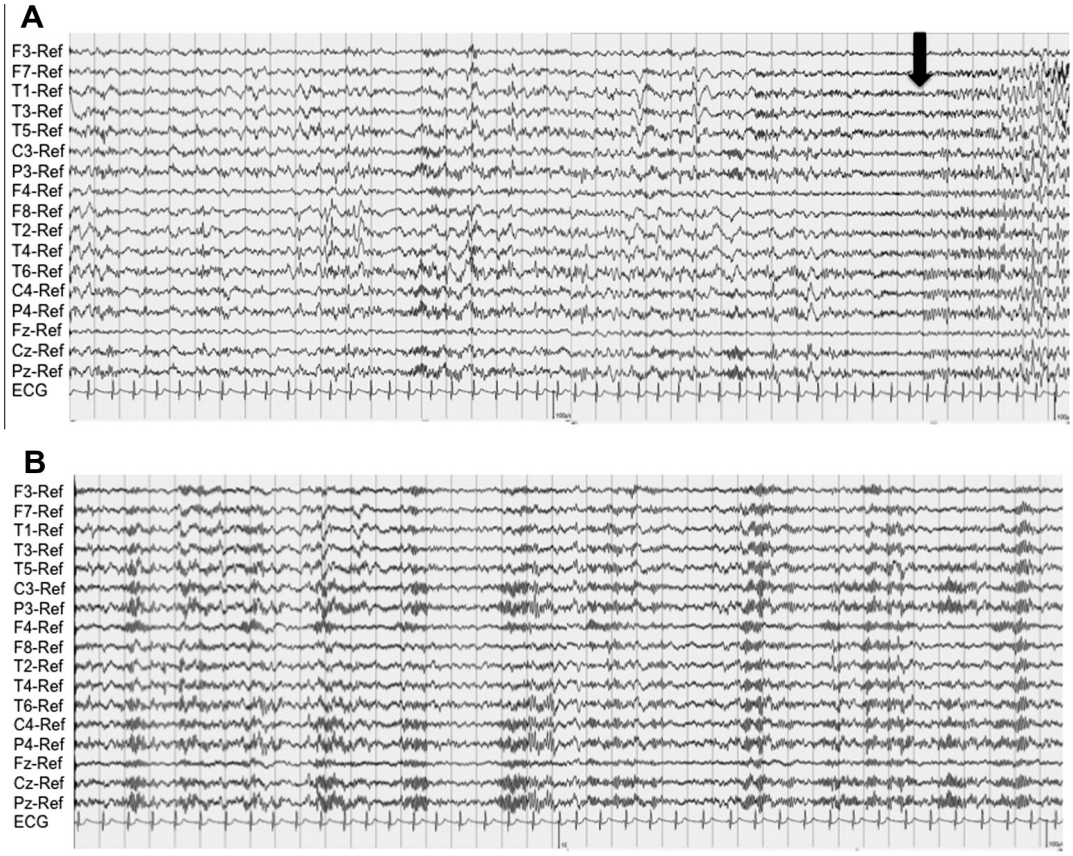

Fig. 1. Preictal and interictal EEG samples. The brief part of 200 s just before the ictal EEG onset (A) and interictal (B) period which were included in the analysis of spindle density and spindle power. If there was an awakening or an arousal period shortly before the seizure onset (black arrow), these periods were not included in analyzing the spindle density. The number of spindles decreased before seizure. (LF:0.3 Hz, HF:70 Hz, sensitivity 10 μV/mm).

4. Results

Of our 42 patients, 24 had TLE (13 female) and 18 had XTLE (9 female). The mean age was 30.5 ± 14.0 years; 32.9 ± 8.2 years for TLE and 29.3 ± 5.1 years for XTLE.

Of the 42 patients, 22 had both, focal and secondarily generalized seizures during sleep (11 both in TLE and XTLE). In the following monitoring days 11 of 42 patients (4 in TLE and 7 XTLE) had 1–5 secondarily generalized seizures during sleep (Total 16 seizures: 4 in TLE and 12 in XTLE) in addition to the first secondarily generalized seizure. Similarly in 22 of 42 patients with both secondarily generalized and focal seizures, 13 patients (5 in TLE and 8 XTLE) had additional 1–2 focal seizures (total 14 seizures: 5 in TLE and 9 in XTLE) during sleep.

The spindle density decreased significantly in all patients in the first focal (10.5 ± 2.5; $p = 0.003$) and generalized preictal period (8.7 ± 2.5; $p = 0.001$) compared to the interictal period (12.2 ± 2.7; Fig. 2). When analyzing the two groups separately, the decrease in spindle densities preictally in first generalized seizures was significant in both the TLE (preictal: 9.4 ± 2.5, interictal: 12.0 ± 2.7, $p = 0.001$; Fig. 3) and the XTLE (preictal: 7.9 ± 2.2, interictal: 12.4 ± 2.7, $p = 0.001$; Fig. 3) group. The difference in spindle density between the first focal preictal period and the interictal period was significant in the XTLE group (preictal: 10.5 ± 2.6, interictal: 12.4 ± 2.7, $p = 0.021$) and showed a trend in the TLE group (preictal: 10.5 ± 2.6, interictal: 12.0 ± 2.7, $p = 0.06$; Fig. 3).

The mean power of spindles in all patients also decreased preictally in first focal (2.3 ± 0.3; $p = 0.04$) and secondarily generalized seizures (2.2 ± 0.4; $p = 0.00$) compared to the interictal period

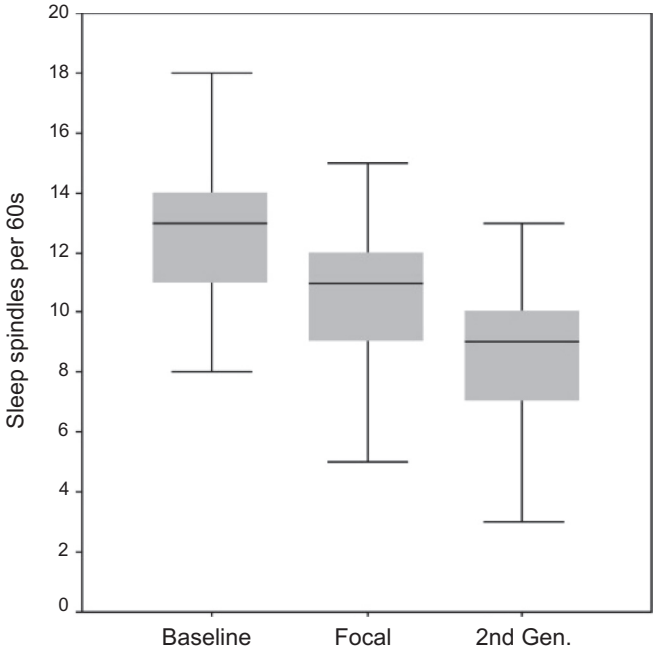

Fig. 2. Change of sleep spindle densities in all patients. Shown are the number of sleep spindles per minute of sleep in all patients comparing baseline sleep, sleep before first focal seizures and sleep before first secondarily ("2nd") generalized seizures.

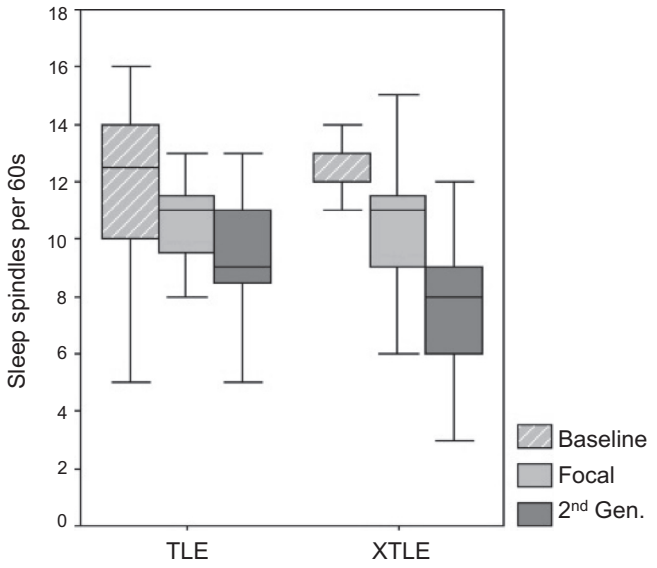

Fig. 3. Change of sleep spindle densities in TLE and XTLE. Shown are the number of sleep spindles per minute of sleep in TLE and XTLE comparing baseline sleep, sleep before first focal seizures and sleep before first secondarily ("2nd") generalized seizures.

(2.4 ± 0.4). Similar to the spindle density analysis, the power of spindle bands decreased preictally in first focal and secondarily generalized seizures in the XTLE group (generalized preictal: 2.2 ± 0.5, focal preictal: 2.3 ± 0.2, interictal: 2.5 ± 0.4; $p = 0.01$, $p = 0.02$). In TLE, though, only the difference of the power of spindle bands between first generalized preictal and interictal periods was significant (generalized preictal: 2.1 ± 0.4, focal preictal: 2.3 ± 0.3, interictal: 2.3 ± 0.4; $p = 0.02$, $p = 0.47$).

In the second part, to check the consistency within a given patient we also investigated the changes of spindle densities in all seizures during sleep.

Similar to findings in the first seizures during sleep, the mean spindle density decreased significantly in all patients in all focal (10.2 ± 1.9; $p = 0.001$) and generalized preictal period (8.8 ± 2.4; $p = 0.001$) compared to the mean of the average interictal period (12.1 ± 2.1). When analyzing the two groups separately, the decrease in mean spindle densities preictally in all generalized seizures was significant in both the TLE (mean preictal: 9.4 ± 2.5, mean-average interictal: 11.8 ± 2.2, $p = 0.001$) and the XTLE (mean preictal: 8.1 ± 2.1, mean-average interictal: 12.4 ± 2.0, $p = 0.001$) group. The difference in spindle density between the all focal preictal period and the average interictal period was also significant in both the XTLE group (mean preictal: 10.0 ± 1.4, mean-average interictal: 12.4 ± 2.0, $p = 0.003$) and the TLE group (mean preictal: 10.4 ± 2.3, mean-average interictal: 11.8 ± 2.2, $p = 0.03$).

The mean power of spindles in all patients also decreased preictally in all other focal (2.3 ± 0.3; $p = 0.05$) and secondarily generalized seizures (2.2 ± 0.4; $p = 0.001$) compared to the average interictal period (2.3 ± 0.2). Similar to the spindle density analysis, the power of spindle bands decreased preictally in all other focal and secondarily generalized seizures in the XTLE group (generalized preictal: 2.2 ± 0.4, focal preictal: 2.4 ± 0.1, interictal: 2.4 ± 0.4; $p = 0.01$, $p = 0.02$). In TLE, though, only the difference of the power of spindle bands between other generalized preictal and interictal periods was significant (generalized preictal: 2.2 ± 0.2, focal preictal: 2.2 ± 0.2, interictal: 2.2 ± 0.2; $p = 0.03$, $p = 0.39$).

5. Discussion

Our study demonstrates that the number and the spectral power of sleep spindles decrease significantly in the immediate preictal period as compared to the interictal baseline in focal and even more so in secondarily generalized seizures. Furthermore, those changes are more pronounced in XTLE than in TLE patients especially in the first seizures during sleep. As a control, all following seizures were investigated to check for consistency, and the difference in spindles remained similar in both XTLE and TLE. The occurrence of spindles should be critically evaluated in subsequent seizures, because of the possible effects of previous seizures on sleep. We speculate that the reduction of sleep spindles heralds seizures because the involved brain structures change their function already ahead of the observable EEG seizure onset.

As sleep spindles have the maximum of their activity over frontocentral regions it is no surprise that more pronounced decreases were seen in seizures arising from the extratemporal lobes in our patients. As a limitation of this study, we could not compare patients with different extratemporal focal epilepsy syndromes because of the limited number of patients in this group, but this should be addressed in further studies.

The relationship of sleep spindles and epileptiform discharges has been studied previously, but not yet in the context of actual seizures in focal epilepsies and not in the immediate proximity around the time of the actual seizure. Epilepsy does affect sleep spindles, as it has been shown that spindle frequency is significantly lower in patients with generalized epilepsy compared to controls and it was also lower in patients with secondarily generalized seizures as compared to patients with complex partial seizures (Drake et al., 1991). Vice versa, the influence of physiological changes of sleep that are illustrated by sleep spindles having a clear effect on epileptiform activity on EEG. Interictal epileptiform discharges (IEDs) are more frequent during times of increased spindles in children with rolandic epilepsy (Nobili et al., 1999) as well as in adults (Ferrillo et al., 2000). The effect of the sleep spindle associated synchronicity on seizures, rather than IEDs, was not specifically addressed in these studies. Only in a restricted group of patients with ADNFLE nocturnal seizures have been shown to be preceded by abnormally prolonged spindles (Picard et al., 2007), suggesting abnormalities in the spindle generating thalamocortical circuit. We do not believe that the results for the ADNFLE patients contradict our results of reduced spindles because this genetic syndrome may indeed by critically different from other, non-genetic, frontal lobe epilepsies.

Supporting our findings related to role of spindles in seizure propensity during NREM sleep, Worrell et al. showed the increased high frequency oscillations (HFO) activity prior to neocortical seizures especially within the seizure onset zone during sleep compared with wakefulness (Worrell et al., 2004). The involvement of thalamocortical oscillations during synchronization are likely a factor in NREM sleep. Similar to HFO, spindles are thought to reflect a higher level of thalamocortical synchronisation and IEDs are more common during times of spindle activity (Ferrillo et al., 2000). We believe that this does not contradict our findings, because the lack of spindles directly preictally may already show the electrophysiological processes before a seizure and an epileptically disrupted network in the frontal lobe may therefore not be able to produce spindle activity any more. We believe, that we should rather consider the inhibitory effect of the preseizure period on spindles than the effect of spindles on seizures in our patients. The decrease of spindle density may reflect the pathophysiology of the epileptic network. On the other end of the thalamocortical connection, lesions to the thalamus will affect seizures in focal epilepsy, typically with a prolongation of the seizure (Bertram et al., 2008). These acquired brain lesions may have an influence on sleep spindles, with mostly a marked decrease in the spindle density (Gottselig et al., 2002), which may be the case in epilepsy patients. We addressed this possible bias by comparing the preseizure spindle density of each patient to the respective interictal density.

Although the reason for the decrease in spindle activity before the onset of secondary generalized seizures cannot be derived from our study, we suggest that it reflects pathophysiologic changes in the epileptic network that reduce the generation of spindles. This may reflect the influence of thalamocortical modulation on seizure generation in focal epilepsies. As these phenomena precede the actual seizures, further studies could address the question, whether this could be used as a warning sign for imminent secondary generalized seizures during EEG-video-monitoring. Furthermore, intracranial recordings of sleep spindles may shed more light on the pathophysiology of the thalamocortical circuit preceding seizures.

Our data demonstrate that the occurrence of seizures and propensity of seizure generalisation in focal epilepsy is modulated by specific characteristics of light sleep such as sleep spindles. This finding supports the notion that changes in the epileptic network precede the seizure onset and have an influence on seizure generation and termination.

Acknowledgement

The authors have no conflict of interest to report.

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